REMARKS

Reconsideration of the present Application in view of the above amendments and the following remarks is respectfully requested. Claims 1, 3-5, and 8-33 are currently pending. The PTO has withdrawn claim 14 from consideration pursuant to 35 C.F.R. § 1.142(b), asserting that it is directed to a non-elected species. Applicants hereby cancel non-elected claims 17-33 without prejudice to prosecution of the subject matter in a related divisional, continuation, or continuation-in-part application. Claims 1, 3-5, 8-13, 15, and 16 are therefore currently under examination. Applicants have amended claim 1 to more clearly define the subject matter encompassed by Applicants' invention. Support for the amended claim may be found in the specification, for example, at page 29, line 18 through page 31, line 6. Furthermore, Applicants thank the Examiner for reconsideration of the Application in view of the Response filed December 9, 2002, and also thank the Examiner for the withdrawal of the rejections based on 35 U.S.C. § 112. In view of the remaining rejections, Applicants respectfully request due reconsideration of the claims in view of the specific remarks as provided below.

REJECTION UNDER 35 U.S.C. § 102

The PTO rejects claims 1 and 3-5 under 35 U.S.C. §§ 102(b) and (e) for lack of novelty. In particular, the PTO asserts that Tonks et al. (WO 98/04712) (§102(b)) and Tonks et al. (U.S. Patent No. 5,912,138) ('138) (§102(e)) each teach a method for identifying an agent that alters the interaction between a substrate trapping mutant PTP and a substrate capable of generating a fluorescence signal. The PTO further alleges that the use of fluorescein or rhodamine in fluorescence techniques, such as fluorescence polarization and fluorescence resonance energy transfer, is known in the art (U.S. Patent No. 6,203,994), and that fluorescence polarization assay techniques are also well known.

Applicants respectfully traverse this rejection and submit that Tonks et al. (WO 98/04712) and Tonks et al. ('138) each fail to anticipate the subject matter of the instant claims. Applicants also submit that the U.S. Patent No. 6,203,994 cited by the PTO provides nothing

more than a cumulative reference in the record in view of those cited in the instant specification insofar as fluorescence polarization is a known method.

Applicants respectfully submit that each of the cited documents fails to teach each and every limitation of the present claims and fails to disclose every limitation in an order that teaches or suggests the presently claimed method. Anticipation requires identity of the invention in the cited document (*see Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 33 U.S.P.Q.2d 1496, 1498 (Fed. Cir. 1995)), that is, every element of the claimed invention must be literally present, arranged as in the claim (*see Richardson v. Suzuki Motor Co., LTD.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)). Applicants submit WO 98/04712 and '138 each fail to teach or suggest a method for identifying an agent that alters the interaction between a protein tyrosine phosphatase (PTP) and a tyrosine phosphorylated polypeptide that is a substrate of the PTP, comprising in pertinent part (a) contacting in solution in the absence and presence of a candidate agent a substrate trapping mutant PTP and a phosphorylated peptide substrate that is capable of generating a fluorescence polarization (FP) signal under conditions that permit formation of a substrate:mutant PTP complex, and (b) comparing in solution without separating the complex from free substrate the FP signal level in the absence of the agent to the FP signal level in the presence of the agent.

WO 98/04712 and '138 each fail to describe using a substrate capable of generating an FP signal to identify an agent that disrupts a binding interaction between the substrate and a PTP substrate trapping mutant. The cited documents also fail to teach or suggest a method that comprises contacting the PTP substrate trapping mutant and a fluorescent labeled peptide substrate in solution and detecting the FP signal in solution. The cited documents refer to a competitive binding assay method that may be performed for identifying an agent that inhibits or enhances the interaction between a PTP and its substrate, for example, by reference in the cited documents to Pawson (U.S. 5,352,660) (cited in '138, at column 9, lines 37-50; cited in WO 98/14712, at page 17, lines 19-32). Pawson only describes isolating a SH2 polypeptide domain or subdomain or an SH2 polypeptide ligand, and then detecting any one of these polypeptide components in an assay in which the component may be labeled with an enzyme, fluorescent material, luminescent material, or radioactive material (Pawson, column 8, lines 38-

58). Pawson also teaches that for use in an assay to detect an antagonist or agonist, any one of the assay components may be insolubilized, for example, by binding to a suitable carrier (*id.*, Column 9, lines 14-38).

Additionally, WO 98/04712 and '138 teach that *either* a PTP *or* a substrate may be labeled with a variety of reporter molecules, including enzymes, radioactive materials, and fluorescent molecules ('138, column 7, lines 7-28; WO 98/14712, page 12, line 27 through page 13, line 13). Such labeled PTP *or* labeled substrate is used, according to the cited documents, in a method for determining the presence of an isolated phosphorylated protein:PTP complex, which is then used to identify a PTP substrate.

By contrast, the presently claimed method comprises contacting a PTP substrate trapping mutant and a phosphorylated peptide substrate in solution. The method does not require any step of rendering one or more assay components insoluble, for instance by solid-phase immobilization, nor does the claimed method require separation of free solutes from those involved in intermolecular binding interactions (*see, e.g.* specification, page 13, lines 16-20). Additionally, the present invention relates in pertinent part to the use of a detectably labeled tyrosine phosphorylated peptide that is a substrate of the PTP and which is capable of generating a FP signal, and *not* to the option of selecting *either* a PTP *or* a substrate for labeling, or of selecting a reporter molecule from an enzyme, radioisotope, *or* fluorophore. Applicants submit that the documents cited by the PTO fail to appreciate or even remotely contemplate the present invention, in which a phosphorylated peptide substrate capable of generating a FP signal is used because of its significantly lower molecular mass relative to a substrate trapping mutant PTP, such that consequently the anisotropic signals of free substrate and substrate complexed with a mutant PTP have measurable differences.

Therefore, the documents cited by the PTO fail to appreciate that a fluorescently labeled PTP would be poorly suited to the assay *in solution* according to the present method. In particular, and as disclosed in the present specification, fluorescence polarization permits measurement *in solution* of the fluorescence anisotrophy in polarized light of a free, fluorescently labeled PTP substrate polypeptide and of the labeled PTP substrate when it is bound to a PTP (*e.g.*, page 29, line 18 through page 31, line 6). FP depends on several factors, including the

extent and rate of rotational diffusion during the excited state of the fluorophore, on molecular size and shape, on solution viscosity, and on solution temperature (*see, e.g.*, page 30, lines 3-8, and reference cited therein). Therefore, low molecular weight fluorophores that are capable of rapid molecular rotation in solution (*i.e.*, low anisotrophy), such as the recited detectably labeled phosphorylated PTP peptide substrate, give rise to low fluorescence polarization readings. When, however, the substrate forms a complex with a high molecular weight molecule such as the substrate trapping mutant PTP, the complex exhibits relatively slow molecular rotation in solution (*i.e.*, high anisotrophy), resulting in higher fluorescence polarization readings. The difference in the polarization value of free, detectably labeled PTP substrate polypeptide compared to the polarization value of a substrate trapping PTP mutant:substrate complex may be used to determine the ratio of complexed (*e.g.*, bound) substrate to free substrate (*see, e.g.*, specification, page 30, lines 20-27).

Applicants submit that the documents cited by the PTO describe methods for labeling either a substrate or a PTP and *requiring* the removal from solution of a substrate/PTP complex as a step in the methods described therein, but fail to describe a method that comprises measuring *in solution* a fluorescence polarization signal of a fluorescently labeled tyrosine phosphorylated peptide substrate, either as free substrate or in a substrate:substrate trapping mutant PTP complex. Use of a PTP substrate peptide capable of generating an FP energy signal is, therefore, neither expressly nor inherently disclosed by either of the cited Tonks et al. documents ('138 or WO 98/04712). *See Continental Can Co. USA v. Monsanto Co.*, 948 F.23 1264, 1268 (Fed. Cir. 1991) (articulating that for a reference to be anticipatory, a gap in the reference may be filled by submitting extrinsic evidence, but the evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill). Applicants further submit that because the cited documents lack a teaching or suggestion of the particular limitations of the instant claims discussed in detail herein, the claimed method does not naturally flow from the disclosure of the Tonks et al. documents. *See id.*, at page 1268-1269 (The mere fact that a certain thing may result from a given set of circumstances is not sufficient; the disclosure must show that it is the natural result flowing from the operation as taught.) (citations omitted).

Accordingly, Applicants respectfully submit that the present claims are novel, thus satisfying the requirements of 35 U.S.C. § 102. Applicants therefore request that the rejection of the claims be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 1 and 8-16 stand rejected under 35 U.S.C. § 103(a), for alleged obviousness over Tonks et al. (WO 98/04712) (Tonks) in view of Jia et al. (*Science* 268:1754-58 (1995)) (Jia). The PTO alleges that a person having ordinary skill in the art would have found it obvious to arrive at the claimed invention by combining (i) the teachings of Tonks that a substrate trapping mutant PTP enzyme-substrate complex can be observed, with (ii) the teachings of Jia that invariant tyrosine at position 46 of PTP-1B interacts with substrate pTyr. The PTO further asserts that an ordinarily skilled person would have been motivated to use the method of Tonks to substitute Tyr46 with a conserved Phe residue to make a PTP1B substrate trapping mutant with a reasonable expectation of success.

Applicants respectfully traverse this rejection and submit that the documents cited by the Action, whether alone or in combination, fail to teach or suggest the subject matter of the instant claims. Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because the cited documents either alone or in combination fail to teach or suggest each and every limitation of the claimed method. As discussed in detail above, Tonks fails to teach or suggest a method for identifying an agent that alters the interaction between a PTP and a tyrosine phosphorylated polypeptide that is a substrate of the PTP, comprising in pertinent part (a) contacting in solution in the absence and presence of a candidate agent a substrate trapping mutant PTP and a phosphorylated peptide substrate that is capable of generating a FP signal under conditions as recited, and (b) comparing in solution without separating the complex from free substrate the FP signal level in the absence of the agent to the FP signal level in the presence of the agent. Tonks fails to teach or suggest using a phosphorylated PTP substrate that is capable of generating a FP energy signal. Tonks further fails to teach or suggest contacting the method components in solution and comparing in solution the FP energy signal in the absence and presence of an agent. Applicants submit that the combined disclosures of Tonks and Jia also fail to teach or suggest each limitation of the present claims. Jia is silent with respect to a method for identifying an agent that alters the interaction between a PTP and a tyrosine phosphorylated polypeptide comprising contacting in solution a substrate trapping mutant PTP and a PTP peptide substrate capable of generating a FP signal and detecting an FP signal in the absence and presence of an agent.

Furthermore, neither Tonks nor Jia provides a teaching, suggestion, or motivation for a skilled artisan to modify their respective teachings to obtain Applicants' invention. As discussed above, Jia is silent with respect to performing any assay to identify an agent that alters the interaction between a substrate trapping mutant PTP and a PTP substrate. Tonks also fails to teach or suggest the desirability of modifying the disclosures therein to obtain a method for identifying an agent that alters the interaction between a PTP and a tyrosine phosphorylated PTP substrate, wherein the method comprises use of a fluorescently labeled PTP peptide substrate capable of generating a FP energy signal and the recited step of comparing FP signal levels. Tonks provides no teaching, suggestion, or motivation for a skilled artisan preferentially to choose to label a PTP peptide substrate for any assay disclosed therein instead of choosing to label a substrate trapping mutant PTP. Rather, Tonks discloses that either the substrate *or* the

substrate trapping mutant PTP could be labeled with any number of different reporter molecules (*see* Tonks, page 13, lines 1-13; page 17, lines 19-32, and reference cited therein). Tonks further fails to provide any teaching, suggestion, or motivation to modify any assay disclosed therein to arrive at a method in which an FP signal may be determined using both the labeled free substrate and the labeled substrate:PTP mutant complex *in solution* without separating free substrate from the complex. Applicants therefore respectfully submit that a person having ordinary skill in the art would not reasonably expect to obtain Applicants' invention successfully by combining the teachings of Tonks and Jia.

With respect to claims 8-16, Applicants submit that the PTO fails to point to any disclosure in either document suggesting the desirability of making such a combination of teachings. *See Teleflex Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002) ("The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence."). Tonks fails to teach or suggest that a substrate trapping mutant PTP as recited, in which the wildtype PTP catalytic domain invariant aspartate residue is replaced with an amino acid, or in which the cysteine that is present in the signature sequence motif is mutated as recited may comprise at least one wildtype tyrosine residue that is replaced with an amino acid that is not capable of being phosphorylated. Applicants also submit that Jia fails to teach what Tonks does not. As discussed further herein and for reasons already made of record, Jia fails to teach *any* method for identifying an agent that alters the interaction between a PTP and a PTP substrate by using a substrate trapping mutant PTP. Jia fails to teach or suggest substitution of the PTP catalytic domain invariant aspartate residue in the catalytic domain of PTP1B to obtain a PTP1B substrate trapping mutant, and further fails to teach or suggest that a substrate trapping mutant may comprise replacement of at least one wildtype tyrosine residue with an amino acid that is not capable of being phosphorylated. Applicants submit, therefore, that Tonks in view of Jia would not have motivated an ordinarily skilled artisan to arrive at the claimed invention.

Applicants respectfully disagree with the assertion by the PTO that an ordinarily skilled artisan would have expected to obtain Applicants' invention successfully by combining the teachings of Tonks with Jia to substitute a phenylalanine residue for a tyrosine residue at

position 46 in a PTP1B substrate trapping mutant. Applicants submit that the PTO has provided no reasoning why a skilled artisan would combine teachings of Tonks and Jia to obtain Applicants' invention (*see id.*; *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (stating that the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed)). Neither Tonks nor Jia provides any teaching, suggestion, or motivation for a method comprising contacting a PTP peptide substrate with a substrate mutant PTP as recited that also has at least one wildtype tyrosine residue replaced with an amino acid that is not capable of being phosphorylated.

Applicants also wish to point out that while Jia suggests that the mechanism of pTyr recognition may be conserved in a PTP because a phenylalanine residue is present in the *Yersinia* PTP at a position corresponding to Tyr46 in PTP1B (*see* Jia et al., page 1755, second column), Jia fails to suggest that substitution of tyrosine with a phenylalanine residue at this position in PTP1B would result in attenuated catalytic activity, which is a characteristic of a substrate trapping mutant PTP (*see, e.g.*, instant specification, page 17, line 18 through page 18, line 18). Because the *Yersinia* PTP has catalytic activity, a person skilled in the art would reasonably conclude that substitution of Tyr46 with phenylalanine in PTP1B would *not* affect the catalytic activity of PTP1B. Therefore, Jia provides no teaching, suggestion, or motivation to mutate Tyr46 or any other tyrosine residue in a PTP to obtain a substrate trapping mutant as recited in the claimed method.

Applicants respectfully submit that for the reasons discussed above, a *prima facie* case of obviousness has not been established, and that the claimed invention is nonobvious as required by 35 U.S.C. § 103. Applicants therefore respectfully request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims remaining in the Application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

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